

## RECENT ADVANCES IN ANTIBIOTIC THERAPY\*†

### FIFTH ANNUAL SYMPOSIUM ON ANTIBIOTICS, WASHINGTON, D.C.

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The Fifth Annual Antibiotics Symposium sponsored jointly by the U.S. Food and Drug Administration and the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy* was held in Washington, D.C., on October 2 to 4, 1957. The meeting was attended by over 800 doctors and no less than 120 papers were presented and 41 others read by title. There were also three panel discussions (*Lancet*, 1957).

The papers, which were read simultaneously in two halls, covered a very wide range of human and veterinary medicine. Thus we heard reports of tetracycline being given to cows by vaginal douche within 24 hours of artificial insemination. An improved fertility rate was noted, and in a New York trial a 66 per cent. conception rate was obtained from one service per animal among 94 so-called "repeat breeders" (Sacchi, Smith, and Tower, 1958). Streptomycin was being used in the State of Missouri for the massive spraying of fruit and vegetables (Logue, Goldberg, and Goodman, 1958). Experiments had been undertaken with streptomycin and tetracycline in an attempt to retard the development of decay in refrigerated pre-packaged spinach (Becker, Goodman, and Goldberg, 1958). It had been estimated that 11 to 13 per cent. of vegetable acreage in the USA was being lost through spoilage during marketing processes, and antibiotics have been widely tested in an attempt to reduce such spoilage. Residues of streptomycin and tetracycline have, however, been detected in treated potatoes, cabbage, and spinach (Goodman, Johnston, and Goldberg, 1958), although tetracycline in potatoes was shown to be lost in cooking. As such antibiotics may persist in treated vegetables for 3 months or more, the possible public health hazards of such processes

are a particular concern of the US Food and Drug Administration.

Experiments designed to prolong the storage life of fresh crab meat with antibiotics were reported as unsuccessful (Benarde, 1958), but 4 to 5 g. per ton of oleandomycin given to chicks in the feed produced a consistent improvement in the growth rate compared with that of untreated birds (Sherman, Donovan, and Reynolds, 1958), thus confirming the findings previously obtained with other antibiotics. That the effects of antibiotics so given was secondary to their anti-bacterial effects was suggested by the findings of Gordon, Wagner, and Wostman (1958), who shewed that untreated chickens not given antibiotics but raised in a germ-free environment had a growth response similar to that of chickens raised in a conventional environment and fed with penicillin. Whether similar growth responses could also occur in humans was investigated by Loughlin, Alcindor, and Joseph (1958), who gave 50 mg. oxytetracycline daily to a group of 243 schoolchildren in Haiti for a period of 12 months without ill-effects or signs of induced staphylococcal resistance in the bowel-carried organisms. Some increase in growth rate was noted in the tetracycline-treated children not suffering from growth failure as compared with the controls. A similar trial was conducted on infants in Brooklyn, New York, who were given up to 50 mg. of oxytetracycline a day for 6 months or more. A slight increase in weight and height was noted in the treated infants over other infants (Litchfield, Turin, and Zion, 1958).

#### New Antibiotics

New developments reported included new anti-fungal antibiotics, derived from soil streptomycetes, *viz.* Amphotericin A and B. These had been applied topically, and a somewhat toxic but soluble form of

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Amphotericin B had been prepared and had been used successfully in five cases of cryptococcal meningitis, a condition which had previously been almost uniformly fatal (Rubin, Lehan, Fitzpatrick, and Furcolow, 1958). Two new antibacterial antibiotics were Ristocetin A and B, given by intravenous injection, which were obtained from the fermentation beer of a new species of actinomycete, *Nocardia lurida*. They were shewn to be effective against Gram-positive organisms, Gram-negative diplococci, and *Mycobacterium tuberculosis*. They were especially useful in cases of staphylococcal pneumonia which were resistant to other antibiotics (Taylor, Schumacher, and Calvy, 1958).

Several improvements were reported with the older antibiotics, such as tetracycline. Hitherto it has not been possible to prepare aqueous solutions of tetracycline hydrochloride containing more than 100 mg./ml., and its use by means of injection in the treatment of venereal diseases has not been practicable. With the new tetracycline phosphate complex, concentrated aqueous solutions containing 250–500 mg. tetracycline hydrochloride per ml. had now been prepared. These could be given by intramuscular injection “with mild or moderate discomfort” and would produce serum levels of tetracycline for 24 hours, which “should be adequate for most susceptible incitants” (Kaplan, Albright, and Buckwalter, 1958).

#### Combined Antibiotics

There was little in the symposium which *directly* concerned the venereal diseases, although a great deal was of indirect importance. Neither syphilis nor gonorrhoea was considered, although the use of tetracycline-oleandomycin combinations in the other venereal diseases was reported in two papers. Loughlin, Mullin, Alcindor, and Joseph (1958b) had successfully used the combination (1.5 g. daily in adults and proportionately less in children) in 106 cases of lymphogranuloma venereum and in 172 cases of yaws. Willcox (1958) described its use in doses of 1 g. daily for six days in non-gonococcal urethritis, and claimed results at least as good—if not better—than those obtained with twelve other substances tested.

It was the introduction of antibiotic combinations such as this which had resulted in controversy at the Fourth Annual Antibiotic Symposium in 1956. The chairman, in his opening remarks, had then said: “It is quite possible that we are now in a third era of antibiotic therapy: the first being an era of the narrow-spectrum antibiotics, penicillin and streptomycin; the second an era of broad-spectrum therapy; the third an era of combined therapy,

where combinations of chemotherapeutic agents, particularly synergistic ones, will be customarily used” (Welch, 1957).

The controversy which followed finally spilled over even into *Life* magazine. Plainly, it concerned problems of microbial resistance which opponents of antibiotic combinations considered might be worsened with their use by broadening the spectrum rather than increasing its depth. They expressed the view that it was preferable to use one antibiotic singly in full doses rather than the reduced amounts inherent in combined preparations. Moreover, the action of oleandomycin to some extent resembled that of erythromycin, and cross-resistance between them might occur (English, 1958). Proponents, on the other hand, considered that encouragement of bacterial resistance was reduced by broadening the spectrum, and that increased depth was obtained by the synergistic behaviour of some antibiotic combinations. Although excellent clinical results have been obtained in many disorders with tetracycline-oleandomycin combinations, the question of synergistic rather than additive action between these antibiotics had by no means been conclusively settled, there being some workers who denied that it occurred (*e.g.* Ross, Zaremba, and Puig, 1958).

#### Resistance to Antibiotics

Resistance to antibiotics is a matter of considerable importance to venereologists at the present time owing to its probable extension into the field of gonorrhoea. It has previously been confined largely to staphylococcal and urinary infections within hospitals, where drug-fast strains are being fostered and spread within closed communities. So far, however, no conclusive evidence is forthcoming to shew that this is occurring in the population at large, either because of dilution when patients are discharged from hospital or because of the widespread use of different antibiotics by general practitioners. Thus, Griffith, Boniece, McGuire, Wolfe, Joiner, Wick, and Holmes (1958) reported that, of 200 members of the public receiving poliomyelitis vaccine at Indianapolis General Hospital during March and April, 1957, 100 carried coagulase-positive *Staphylococcus aureus*, 193 *Staphylococcus albus*, and three *Staphylococcus citreus* in the nose and throat, or both. Of these so-called “street staphylococci”, approximately 28 per cent. of the *S. albus* and 70 per cent. of the *S. aureus* strains were sensitive to penicillin. Of the *S. aureus* strains, 100 per cent. were susceptible to chloramphenicol, erythromycin, and vancomycin, and 97 per cent. were susceptible to novobiocin and tetracycline.

There was some support at the Symposium for the following principles which are already applied in some hospitals to cope with the problem of bacterial resistance to antibiotics:

- (1) Rigid asepsis and the avoidance of catheterization wherever possible;
- (2) Restraint in the use of antibiotics and the avoidance of prophylactic antibiotics except on well-established indications;
- (3) Complete restriction of one antibiotic to use in serious cases (*e.g.* staphylococcal septicaemia) due to organisms resistant to other antibiotics.

Incidentally it was reported by Kass and Ziai (1958) that methionine in doses of 200 mg./kg. per day in divided doses was very helpful in reducing the bacterial counts in antibiotic-resistant urinary infections due to *A. aerogenes*, *B. proteus*, and *B. coli*.

### Reactions to Antibiotics

Of particular interest were a paper presented by the chairman of the Symposium, Dr. Henry Welch of the US Food and Drug Administration, on penicillin reactions, and other reports of a promising new preparation with which to combat them.

Welch and his colleagues had previously made a survey in 1952 and 1953 in eleven large cities with a population of 100,000 or more, and had discovered 88 cases of anaphylactic shock, of which 25 (28 per cent.) had proved fatal (Welch, Lewis, Kerlan, and Putnam, 1953). He now reported a much wider investigation covering the 4-year period 1953–1957 (Welch, Lewis, Weinstein, and Boeckman, 1958). This latter survey was designed to include more than 800 hospitals and to interview 1,600 physicians. By using Inspectors of the Food and Drug Administration in the different districts, a survey was made in some detail of all severe reactions of every character to all antibiotics. In fact, some 827 general hospitals were covered, with 198,332 beds, representing approximately 29 per cent. of the total number of hospital beds in the entire United States. Altogether 1,070 life-threatening reactions were discovered, in addition to 1,925 non-life-threatening cases, mainly of angioneurotic oedema.

Of the 1,070 life-threatening cases, 809 were of anaphylaxis, of which 793 had followed the use of penicillin in some form, given by intramuscular injection in 733 cases. They were divided approximately equally between men and women. Only sixteen instances of anaphylaxis had been noted after other antibiotics, including streptomycin, chloramphenicol, and the tetracyclines. Fatalities occurred in two of the latter group (both following streptomycin) and in 63 of the penicillin-treated

group; all these fatalities followed intramuscular injection. There were no fatalities in the sixty cases in which anaphylaxis occurred after penicillin given other than by intramuscular injection. The incidence of anaphylactoid reactions had increased each year during the survey. The general fatality rate was 9·1 per cent., a considerable improvement on that encountered in the 1952–53 survey. This perhaps reflects a greater awareness of penicillin anaphylaxis and a more ready availability of resuscitative measures.

The next largest group of life-threatening reactions was that of super-infection of which there were 107 cases with forty fatalities. In 99 instances the complication was entero-colitis, which accounted for 39 of the deaths. In 74 instances the complication was proved to be staphylococcal and in 59 instances it followed abdominal operation. Although one case each followed the use of penicillin, erythromycin, and neomycin respectively, and eleven cases followed the use of combined antibiotics other than the tetracyclines, these last were responsible for the remaining 85 cases. There were eight cases of severe moniliasis (four intestinal, two dermal, and two pulmonary), two of which followed penicillin, one combined antibiotics, and five the tetracyclines. One of these patients died.

There were seventy cases of severe skin reaction (51 of exfoliative dermatitis, sixteen of purpura, and three of erythema multiforme), seven of which proved fatal; 46 of these followed the use of penicillin, and five of these were fatal. Blood dyscrasias were also reported in 46 cases, and chloramphenicol had been used alone or in combination in 41 of them; there were 27 deaths (more than 50 per cent.), 25 of which had followed the use of chloramphenicol, one tetracycline, and one novobiocin (penicillin and sulphonamides). There were also 38 life-threatening cases of angioneurotic oedema, 37 with severe respiratory involvement and one with cerebral involvement; 37 of these followed the use of penicillin and one intramuscular chloramphenicol. There were five deaths in this group (13 per cent.).

Penicillin was obviously the drug principally involved, being responsible for 901 (84 per cent.) of the 1,070 life-threatening reactions. This antibiotic was also responsible for 1,616 of the 1,925 reactions not classified as life-threatening (83·9 per cent.).

If the problem of penicillin reactions appears at first sight serious, it must be related to the enormous amount of antibiotics used. In the USA in 1956 some seventeen different antibiotics were clinically available and about 2,500,000 pounds of antibiotics were produced. Penicillin accounted for 38 per cent. of this total and no less than 121 penicillin preparations

were commercially available. In fact, some 900 tons of penicillin were manufactured during the period of the survey, or 400 tons if human medicine alone was considered—enough for 2 billion doses each of 300,000 units! The size of the U.S. antibiotic industry is staggering. Its dollar value has expanded in only 13 years from zero in 1942 to 300 million at the manufacturers' level in 1955 (Welch, 1957).

### Penicillinase

A most promising development was the clinical use of penicillinase. This bacterial enzyme is secreted by many strains of bacteria, including *Escherichia coli*, *Bacillus cereus*, and some staphylococci. Although discovered in 1940, its use was restricted until 1956 to its *in vitro* antagonism to the antimicrobial effect of penicillin in various bacteriological procedures. It is a thermolabile protein which hydrolyses penicillin to inactive penicilloic acid.

Zimmerman (1958) reported that penicillinase had proved completely non-toxic and non-antigenic in guinea-pigs and human volunteers. Twenty humans were then given 800,000 units fortified penicillin twice daily. Single injections of 100,000–800,000 units penicillinase were given to these persons and, *within one hour* and afterwards for periods of 4 to 7 days, no circulating penicillin could be discovered in spite of the fact that the injections of penicillin were still being continued. Animal experiments conducted by Chen, Bard, and Belsito (1958) indicated that a single dose of 5,000 units penicillinase effected complete inactivation of 100,000 units of crystalline potassium penicillin given within the first 8 hours after penicillinase, and a considerable inactivation of similar doses of penicillin administered during the second and fourth days. A "unit" of penicillinase is defined as that amount inactivating 1 unit penicillin per minute at 25°C., pH 7, *in vitro* (Zimmerman, 1958).

Injections of penicillinase were given to 52 patients with penicillin reactions by Zimmerman (1958). No cases of anaphylactoid reactions were included in this series, which comprised mainly cases of chronic urticaria and a serum-sickness-like syndrome in which many antihistaminic drugs and steroids had been used without success. Clearance of signs and symptoms was complete in 46 cases after only one to three injections, and there was some doubt whether penicillin was responsible in the few patients whose condition failed to respond. Similar findings were reported in a second series of 46 cases by Becker (1958).

Since then penicillinase has appeared on the American commercial market under the proprietary

name "Neutrapen", manufactured by Schenlabs Pharmaceuticals Inc. of New York. Apart from local pain, which occurs in about one-third of cases unless the injections are given deeply into the muscle, the preparation is largely free from side-effects, although a case with a morbilliform rash has been reported (Zimmerman, 1958). For this reason no attempt is now made to equate the required dose of penicillinase to the dose of penicillin which has been given, and an intramuscular injection of 800,000 units is recommended as soon as possible after symptoms of a penicillin reaction appear; if necessary this may be repeated at 3 to 4 day intervals. In anaphylactic reactions, it is recommended that 800,000 units should be given intravenously, and immediately followed by 800,000 units intramuscularly. There is so far insufficient evidence to evaluate the effects of penicillinase in anaphylactic reactions, and it is obvious that adrenaline and the more urgently required drugs should be used first—but penicillinase may well supplant the use of steroids. Penicillinase is supplied in single-dose vials containing 800,000 units in powder form which is stable at room temperature.

One of its possible uses apart from the treatment of penicillin reactions is to prevent them. It is suggested that it should be given to penicillin-sensitive or allergic persons when they are given drugs or vaccines (notably poliomyelitis vaccine) containing minute traces of penicillin. Also it may be useful diagnostically in patients with skin eruptions where penicillin is only one of several possible exciting allergens. Another potential valuable use in venereology is for the cutting off of the lower levels of declining penicillinaemia at some time to be agreed after therapy for gonorrhoea, so as to prevent the fostering of resistance. Indeed, this principle could be applied to all uses of penicillin in all diseases.

Certainly many will concur with Becker (1958) that "... just as adrenaline is on hand in every doctor's office and hospital for anaphylactic reactions, penicillinase should also be on hand in every doctor's office and hospital where penicillin is used, to help prevent such tragic anaphylactic accidents".

### Indiscriminate Use of Antibiotics

The problems of bacterial resistance and human sensitization to antibiotics can both be reduced by discouraging the indiscriminate use of antibiotics, which are not infrequently given for trivial and even unspecified conditions such as "tired blood" and "one-degree under". This point was well made by Jawetz (1958) in the first Randall Lecture. These

lectures, which are to become a permanent feature of these Symposia, are given in honour of Dr. W. A. Randall, who had worked with the U.S. Federal Agency for many years, had delivered the Almroth Wright Lecture in London and the MacArthur Lecture in Edinburgh, and who died last year (Dowling, 1958). Jawetz, whose main thesis was to identify the target before discharging the antibiotic blunderbuss, and then to hit it hard with the minimum of overlap, gave a striking example published by Nolen and Dille (1957) of the degree to which antibiotics have been used in the U.S.A. In Igloo, North Dakota—a very small town or large village of only 793 residents—only sixty persons (7.9 per cent.) had failed to receive antibiotics during a 5-year period. Moreover, even by the most lenient criteria, such antibiotic therapy was warranted for less than half of the 2,936 separate illnesses or complaints which had been treated with these drugs.

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